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BMJ Open Protein-enriched, milk-based supplement to counteract sarcopenia in acutely ill geriatric patients offered resistance exercise training during and after hospitalisation: study protocol for a randomised, double-blind, multicentre trial

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ABSTRACT

Introduction Age-related loss of muscle mass and strength, sarcopaenia, burdens many older adults. The process is accelerated with bed rest, protein intakes below requirements and the catabolic effect of certain illnesses. Thus, acutely ill, hospitalised older adults are particularly vulnerable. Protein supplementation can preserve muscle mass and/or strength and, combining this with resistance exercise training (RT), may have additional benefits. Therefore, this study investigates the effect of protein supplementation as an addition to offering RT among older adults while admitted to the geriatric ward and after discharge. This has not previously been investigated.

Methods and analysis In a block-randomised, double-blind, multicentre intervention study, 165 older adults above 70 years, fulfilling the eligibility criteria, will be included consecutively from three medical departments (blocks of n=20, stratified by recruitment site). After inclusion, participants will be randomly allocated (1:1) to receive either ready-to-drink, protein-enriched, milk-based supplements (a total of 27.5 g whey protein/day) or isoenergetic placebo products (<1.5 g protein/day), twice daily as a supplement to their habitual diet. Both groups will be offered a standardised RT programme for lower extremity muscle strength (daily while hospitalised and 4×/week after discharge). The study period starts during their hospital stay and continues 12 weeks after discharge. The primary endpoint is lower extremity muscle strength and function (30 s chair-stand-test). Secondary endpoints include muscle mass, measures of physical function and measures related to cost-effectiveness.

Ethics and dissemination Approval is given by the Research Ethic Committee of the Capital Region of Denmark (reference no. H-16018240) and the Danish Data Protection Agency (reference no. HGH-2016-050). There are no expected risks associated with participation, and each participant is expected to benefit from the RT. Results will be published in peer-reviewed international journals

Strengths and limitations of this study

- To our knowledge, this is the first study to investigate the effect of protein supplementation in addition to resistance exercise training (RT) among acutely ill geriatric patients while admitted and after discharge, and it adds new information to the evidence-based healthcare.
- The study is randomised and double-blinded which minimises the risk of selection, performance and detection bias, and the multicentre trial design increases the generalisability of the results.
- The lack of supervised RT after discharge might lower compliance to the RT, although it is more realistic that self-training at home can be implemented in a real-world setting.
- Acutely ill older adults are a difficult population to maintain in a long-duration intervention study, which increases the risk of dropouts and/or low compliance.
- Registration of compliance in dietary studies is always associated with a risk of bias, but by asking the participants to register their daily intake, save empty bottles and by calling them on a weekly basis to check on compliance, this is minimised.

and presented at national and international congresses and symposiums.

Trial registration number NCT02717819 (9 March 2016).

INTRODUCTION

Sarcopenia is the loss of muscle mass and strength with ageing. It is an unavoidable process with a multifactorial aetiology^{1,2} associated to impaired balance and increased risk of falls and mortality.³ Also, sarcopenia

is associated with a threefold to fourfold increased risk of disability, which in turn is related to substantial socio-economic and healthcare spending.⁴ Acute illness might result in stress metabolism that further increases the loss of protein and the anabolic resistance in older adults, leading to increased loss of lean body mass (LBM),⁵ and this is further accelerated by bed rest during hospitalisation. Also, many older adults consume relatively small amounts of protein, important for maintenance and build up of LBM, and loss of appetite as a consequence of acute illness may further decrease the protein consumption.^{6,7} This is very critical, as research has shown that the protein requirement increases with age.⁸ Even a short hospital stay increases the risk of losing functional capacity and the ability to cope with activities of daily living.⁹ For older medical patients, it has been shown that only one in three regained their habitual physical function 1 year after discharge.¹⁰ Hence, interdisciplinary interventions to counteract sarcopenia become even more relevant in the acutely ill older patients.

The beneficial effect of resistance exercise training (RT) on counteracting sarcopenia is quite well established,^{11,12} and the effect of protein supplementation alone has also been documented.¹³ Less well studied is the potential benefit of a higher protein intake or supplementation as an addition to offering RT among older adults. A recent systematic review by Malafarina *et al*¹³ and a meta-analysis by Cermak *et al*¹⁴ have concluded that in older adults, protein supplementation increases muscle mass, and in some studies also muscle strength, during prolonged RT.^{13,14} However, the evidence is sparse in the frailest older adults, who often have a low dietary protein intake, and based on findings in systematic reviews, they might benefit even more from a combined intervention.^{14–16} To our knowledge, no studies have yet investigated the effect of protein supplementation in addition to offering RT among hospitalised, acutely ill old adults — a population at great risk of a rapid functional deterioration. Thus, the present study aims at investigating this, and in addition, the intervention will continue after discharge from the hospital. The novelty of this study is twofold. First, the intervention involves hospitalised older adults, and second, the intervention continues after discharge. To the best of the authors' knowledge, previous studies were only performed in one setting.

METHODS AND ANALYSIS

Study design

The study design is a block-randomised, double-blind, placebo-controlled, multicentre intervention study. A total of 165 participants will be included consecutively from the medical departments of three hospitals in the capital region of Denmark (Gentofte and Herlev University Hospital and Rigshospitalet-Glostrup, $n=55$ from each place). Recruitment takes place a maximum of 72 hours after admission. After inclusion, participants will be randomly allocated (1:1) to receive either

protein-enriched, milk-based supplements (whey protein) or an isoenergetic placebo product, as a supplement to their habitual diet. Both groups follow the same RT programme and are daily supplemented with vitamin D. The intervention starts at the hospital while admitted and continues 12 weeks after discharge. Recruitment and data collection started in April 2016 and will end in June 2018.

Study population

Inclusion criteria for participation are: men and women aged ≥ 70 years, able to speak and understand Danish, expected length of stay >3 days (evaluated by medical staff at the department), ability to stand independently for at least 30 s and admission to the medical departments of Gentofte Hospital, Herlev Hospital or Rigshospitalet-Glostrup. Exclusion criteria are: active cancer, renal insufficiency ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$), cognitive impairment (not able to comprehend the purpose of the study/give informed consent), terminal disease, exclusively receiving enteral or parenteral nutrition, milk/lactose allergy or intolerance, planning to lose weight/go on a special diet, planned transfer to other hospitals/departments and pacemaker/other implanted electrical stimulants (due to Bio-Impedance Analysis (BIA) measurements). Participants will be withdrawn from the study if they die during admission (does not apply to subsequent admissions) or are discharged/transferred from the medical department before the intervention has started.

Randomisation and blinding

After collection of baseline measurements and characteristics, participants are randomised to either the intervention or the control group using sealed, opaque envelopes containing a paper with either an 'A' or a 'B'. Each hospital site has its own pile of envelopes in order to allow for block randomisation. Within each site, 10 A's and 10 B's (20 in total) are put in the pile over three rounds to ensure a more even allocation of participants in the two groups at any time. Participants, hospital staff and study investigators will all be blinded towards the randomisation. If a situation arises where unblinding may be considered for the benefit of the participant, this will be decided on an individual basis taking the specific situation into account. Enrolment and randomisation are performed by study investigators.

Intervention

Protein-enriched, milk-based supplements and placebo

Depending on their allocation, participants will receive either a protein-enriched, milk-based supplement beverage (Arla Foods: 781 kJ, 10.5 g whey protein concentrate and 0.5 g casein, 10 g fat and 13 g carbohydrate per 100 mL) (intervention group) or an isoenergetic placebo beverage (Arla Foods: 797 kJ, 0.6 g protein, 10 g fat and 24 g carbohydrate per 100 mL) (control group). The amino acid profile of the intervention product is



shown in online supplementary table 1. Both products have a flavour of raspberry and come in ready-to-drink preparations. From January 2017 and on, the protein-enriched, milk-based supplement will have vitamin D added in amounts of 1.125 µg per 100 mL. During the whole study period (while hospitalised and 12 weeks postdischarge), the participants will be instructed to drink a total of 250 mL per day, divided into two servings of 125 mL. Thus, the intervention group will get a total of 27.5 g extra protein per day, equal to 26.25 g whey protein containing a total of ~2.5 g leucine. This amount of protein supplementation is chosen, based on previous studies finding positive effects from similar or smaller dosages.^{17–19} Furthermore, protein supplementation is satiating, and if given in higher amounts, might compromise habitual food intake to a great extent, especially among older adults with low appetite. The total dosage is divided into two servings (breakfast and next cold main meal), as research indicate that 25–30 g of high-quality protein is needed per main meal to maximally stimulate postprandial protein synthesis.⁸ The beverages come in white bottles with either a 'group A' or 'group B' label. While hospitalised, the timing of the intake is as follows: one serving at breakfast (or at lunch, if not consumed at breakfast for any reasons, for example, fasting necessary, or if the RT is performed right after breakfast) and one serving directly after the RT. In the 12 weeks after discharge, the participants will be instructed to drink one serving at breakfast and one serving with the next cold main meal, irrespective of the meal is eaten at lunch or at dinner time. If the participants forget to drink the beverages at the specific times, they will be told to drink it when they become aware of it. The participants will not be instructed to make other dietary changes during the study period. If participants are prescribed/recommended by hospital staff to take oral nutritional supplements, this is not an exclusion criterion, but participants will be instructed to take any additional supplements on a given day only after intake of the 'study beverages'. If for some reason (eg, uncontrolled diabetes or severe reduction of habitual food intake) the participant is advised by medical doctors/nutritional therapists to stop taking the supplement, this advice will always be followed.

Vitamin D supplements

Vitamin D supplementation has been shown to have an independent effect on muscle.²⁰ To reduce the potential confounder of a large difference in intake of vitamin D between groups, all participants will get vitamin D supplements handed out after enrolment and be instructed to take a supplement of 20 µg/day (two tablets of 10 µg), as recommended by the Danish National Board of Health.²¹ Exceptions to this are those participants whose serum vitamin D levels have been measured to ≥100 nmol/L at the time of study inclusion to avoid reaching toxic levels. The participants have to register their intake of vitamin D in a diary along with their intake of the intervention products. Also, at the last visit in study

week 12, the number of tablets left in the container will be counted to verify the registrations. If participants already take vitamin D supplements in combination tablets with other vitamins and/or minerals corresponding to 20 µg/day or more, they will be instructed to keep taking their own tablets and register this. The exact amount of vitamin D in these tablets will be recorded. An average intake of vitamin D per day during the intervention period will be used to compare if the intake of vitamin D is different between the two groups.

Resistance exercise training

The RT programme is developed by experienced physiotherapists and is consistent with the official statements from the American College of Sports Medicine on recommendations for RT in older adults.²² It focuses on strength training primarily of the big muscle groups of the lower limbs and can be performed without any training equipment. One training session consists of three exercises: 'lifting-and-lowering the pelvic' from a crook-lying position, 'sit-to-stand from a chair' and 'lifting-and-lowering the heels' in a standing position, that is, performing heel-raises. All exercises are performed in three sets, aiming at 10 repetitions, pursuing an intensity of 8–12 repetition maximum. The repetition velocity will be performed at the participants own preferred speed. There will be a time interval of 1–3 min between sets and exercises, depending on the individual need for rest. Each of the three exercises can be performed in five different modes (A–B–C–D–E), graduated in terms of increasing resistance, by applying the participants' own body weight and different starting positions. Thus, the programme can be individualised corresponding to the participants' abilities, and adjustments will be made to ensure progression. The illustrated RT programme can be seen in online supplementary figure 1. Participants can be asked to leave out a specific exercise if there are safety concerns (eg, severe dizziness or worsening of a condition) or if they experience pain related to performing a certain exercise.

While admitted to hospital, supervised RT is offered daily by physiotherapists in addition to the standard of care. After discharge, the participants are encouraged to perform the same RT programme as self-training four times per week. They will be instructed to have at least 24 hours between training sessions. During the hospital stay, it is expected that the participants have a very limited amount of physical activity besides the RT programme offered and that the intensity by which they can perform the RT is rather low. This is why the frequency of the RT differs between the hospital and discharge setting. To instruct the participants in regard to the RT and to ensure progression (or regression if necessary), they receive follow-up home visits by a physiotherapist in study weeks 1, 3, 6, 9 and after discharge from any readmissions. The adjustments are made after standardised procedures.

Participants who are discharged with a plan of rehabilitation including ambulatory training at a centre or supervised training at home, to be provided by their municipally,

will be asked to perform the full RT study programme until their rehabilitation programme starts up (a wait of 2–6 weeks is normal). Each training session performed as part of a rehabilitation programme will replace *one* self-training session of the RT study programme. The same applies if participants are discharged from the hospital directly to a 24-hour rehabilitation centre and they are performing RT in their regimen. This is to allow for proper restitution. The offer of supervised training applies only to the first hospital stay, but if readmitted to hospital, participants will be encouraged to do the RT themselves to the extent possible.

Compliance

While hospitalised, the participants will get the product handed out along with the vitamin D supplements. Investigators and physiotherapists register overall study compliance, that is, daily ingestion of the intervention or placebo supplements (time for handout and amount ingested), vitamin D (dose, yes/no) and performance of the RT (number of sets and repetitions for each exercise). Empty bottles are saved so that study investigators can verify the amount of intervention product consumed.

After discharge, the amount of intervention or placebo supplement consumed, and the RT performed for each participant will be assessed by daily records in a 'beverage and exercise diary', specifically designed for the study and handed out to be filled in by the participants. The participants, for example, with help from their relatives, are asked to daily register the amount of beverage consumed: 0%, 25%, 50%, 75% or 100% of each of the two servings by ticking of the corresponding circular illustration, along with ticking of the intake of vitamin D. Participants also have to register execution of the RT and specify for each of the three exercises the number of sets and repetitions performed. If they are exercise training at a rehabilitation centre, this can be registered in the relevant boxes. In case of deviations, four prespecified explanations are given that they can tick off, both in regard to the intake of supplements and the execution of the RT. To verify the participants' records, they are asked to save and store empty bottles, which will be picked up by investigators on days with home visits. At the same time study investigators will help the participants to retrospectively fill out any missing registrations. Participants who are discharged to a 24-hour rehabilitation centre will get the intervention products handed out by the staff who will also save empty bottles. On the first visit after discharge, the participants will receive thorough instructions on how to register compliance in the 'beverage and exercise diary', and upcoming visits will be planned. Both groups will receive daily standard messages on their cell phone (if they have one and agrees to this) and weekly phone calls, kindly reminding them to consume the supplement and vitamin D, perform the RT and register compliance. Furthermore, as part of the phone call, they will be asked about compliance and any deviations or, for example, upstart of training at a rehabilitation centre will be registered and

validated/compared later on with their own diaries, and they will be reminded of upcoming home visits.

Outcome parameters

The baseline characteristics will be collected at inclusion to the study. To standardise the endpoint measures, especially that of LBM, these will be assessed 1.5–2 hours after a light breakfast. Thus, if inclusion happens in the afternoon, then baseline measurements will be assessed the following day, prior to any study interventions. The measurements will be assessed in a predefined order to reduce fatigue and follow standardised procedures, and they will be repeated within 72 hours after discharge and 12 weeks (± 2 days) after discharge. If possible, before each endpoint examination, the participants will be asked to consume a breakfast, similar to that consumed at the hospital before the baseline measurements. The assessments after discharge will be performed in the participants' own home. Follow-up assessments, including only admission to hospital and mortality, will be assessed 6 months after the intervention period. In general, if participants are readmitted to hospital, if possible, assessments will be performed there and otherwise at a replacement visit after discharge. All data collection is performed by study investigators. [Table 1](#) gives an overview of the study period and the different time points for meetings and tests.

Primary endpoint

Lower extremity muscle strength is measured by the 30s chair-stand-test (30s CST). The test exists in both a standardised and a modified version. The standardised 30s CST measures the number of times the participant can rise and sit from a standard chair (height of 43–45 cm) in 30s with the arms folded across the chest, starting from a sitting position. Only full stands will count, that is, full extension of the knees and hips. Those who cannot stand from the chair without using the arm rest will get a score of 0.²³ In the modified 30s CST, the participant is allowed to use the arm rests.²⁴ If participants are only able to perform the modified version at baseline, for the following assessments, they will be asked to do the same. If they are able to do the standardised version, they will be asked to do that as well after a 15 min rest. A change of 2.0–2.6 stands is considered to be clinically relevant based on data from a population of older adults with hip and knee osteoarthritis.²⁵

Secondary endpoints

Total, appendicular and trunk LBM (kg and per cent) is assessed by Bio-Impedance-Analysis (BIA) using the portable InBody-230 body composition analyser (dual frequency (20 kHz and 100 kHz), tetra polar 8-Point Tactile Electrode System (InBody, Copenhagen, Denmark)). Direct segmental measurement technology is used, meaning that no calculations, and thus empirical factors and imputations, are needed. Various factors can affect BIA measurements such as previous exercise, body position,

**Table 1** Flow chart of the study period, including meetings and tests

Flow chart of study period	Baseline	Inhospital intervention	Posthospital intervention*					Follow-up
Study week no.	–	–	1	3	6	9	12	38
Meetings including tests	1+2	–	3	4	5	6	7	–
Inclusion and exclusion criteria	X							
Informed consent	X							
Baseline characteristics	X							
Baseline endpoint assessment†	X							
Randomisation	X							
LOS (inhospital intervention period)		X						
Dietary registration		X (4 days in total)						
Daily compliance registrations		X			X			
Endpoint assessment‡			X‡				X§	
Exercise adjustments			X	X	X	X		
Weekly phone call					X			
24-hour dietary interview				X	X	X	X	
Exercise interview				X	X	X	X	
Evaluation questionnaire							X	
Delivery of intervention products		X (ongoing basis)			X (deliveries after appointment)			
Collection of empty intervention bottles			X	X	X	X	X	
Readmissions, LOS and mortality							X	X

*Assessed 1.5–2 hours after a light breakfast (preferably the same meal every time).

†Assessed within 72 hours after discharge.

‡Assessed 12 weeks (±2 days) after discharge.

§Assessments and meeting are taking place where the participants live.
LOS, length of hospital stay.

skin temperature, dietary intake and hydration state.²⁶ Thus, in order to standardise the measurements, these will be performed in the morning 1.5–2 hours after a light breakfast and bladder emptying (preferably also bowel emptying) and before any exercise. Participants will be asked to wear light clothes and no shoes. They will be instructed to stand upright with the feet on the build-in electrodes embedded in the scale platform, grasp the handles of the analyser while spreading the arms as much as they can and look straight ahead. The reliability of the InBody-230 body composition analyser will be measured and used to establish the threshold of change needed beyond measurement error.

Hand grip strength (HGS) is a proxy measure of upper extremity strength and is measured in kg using the second handle position with a DHD-1 Digital Hand Dynamometer (Saehan Medical, 2012, Roskilde, Denmark). The second handle position is recommended as a standard position, as it is suitable for most hand sizes. An investigator will instruct the participants to be seated with their feet on the ground, shoulders adducted and neutrally rotated, elbow flexed at a 90° angle and supported on the armrests of the chair or a table and forearm and wrist in neutral position, as recommended by Roberts *et al.*²⁷ They will be asked to perform three maximum force trials

with their dominant hand, and the highest value will be registered. They will be instructed to squeeze the handle as hard as they can for 5 s, and the test will be repeated within 15 s.

Four-meter gait speed (4m GS) is used to assess the usual gait speed (m/s) over a short distance. Participants will be placed behind a starting line and instructed to start walking at their usual pace after the investigators command. To reduce the effect of acceleration and deceleration, each participant will be instructed to walk towards a visual goal for 5 m. The time will be started after the participant has walked 0.5 m and stopped after 4.5 m, counted from the first footstep that crosses the 4m start line and end line, respectively. The fastest of two attempts is recorded. If it is not possible to establish a 5 m test track, a shorter track with a minimum length of 3.5 m in total will be used instead, and this will be registered as bias.^{28 29} The participants are allowed to use a gait aid, which will be registered as well. In sedentary older adults, a clinical relevant difference is found to be 0.03–0.05 m/s, while 0.08 m/s is found to be a substantial relevant difference.³⁰

Functional ability is measured using the modified Barthel Index (Barthel-100).^{31 32} The Barthel-100 contains 10 measures of everyday and mobility activities, and the ability to master these activities reflects the level of

functioning. Each measure has five levels of functioning, and for all 10 measures, a maximum of 100 points can be achieved, corresponding to fully independent. The Barthel-100 will be scored by the investigators and rated based on the amount of assistance required to complete each activity or by observing, and clarifying questions will be asked when necessary.

Mobility is assessed by De Morton Mobility Index (DEMMI), which provides a 15-item unidimensional measure of mobility across the spectrum from bed bound to independent mobility, specifically developed for geriatric patients.³³ It has five categories in which the participants are tested: bed (three test scores), chair (three test scores), static balance (four test scores), walking (two test scores) and dynamic balance (three test scores). A total test score from 0 to 19 can be achieved, and this raw score is converted to an interval DEMMI score from 0 to 100, where 100 represents independent mobility. In older acute medical patients, the clinical relevant difference is found to be 10 points on the converted scale.³³

Cognitive function is measured using the Mini-Mental State Examination (MMSE), which consists of small simple tasks to elucidate eight different cognitive functions: orientation, episodic memory, concentration, function of language, practical exercise, reading skills, writing skills and visual-spatial construction. The performances are scored to give a raw score ranging from 0 to 30, where 30 represent the best/optimal function.³⁴

Social support is evaluated using registrations of home care (yes/no; if yes, then divided into practical help, personal care and both) and residence (own home, nursing home/assisted living facility and 24-hour rehabilitation facility).

Use of gait aid is registered as yes (including specific gait aid), no or cannot walk.

Length of hospital stay (LOS) corresponds to the in-hospital intervention period (days from recruitment until discharge), which is registered from the electronic patient register.

Readmission to hospital and mortality: readmission to hospital is registered both with regard to frequency and the total LOS from the electronic patient register. These data are summed up after the intervention period and after the follow-up period, respectively.

Health-related quality of life (QOL) is assessed by using the generic questionnaire, EuroQol-5Dimensions-3Level (EQ-5D-3L).³⁵ The questionnaire is self-reported and reflects the participant's current situation.

Scores for the EQ-5D-3L are generated from the ability of the individual to function in five dimensions: mobility, pain/discomfort, self-care, anxiety/depression and usual activities. Each dimension has three possible answers: no problem, some problems and major problems. Also, the participants rate their current health state on a visual analogue scale ranging from 0 to 100 (reflecting a health state from 'worst' to 'best').

Body weight is measured to the nearest 0.1 kg using the BIA equipment InBody-230 and follows the same

standardised procedures as described under the endpoint 'muscle mass'.

Product evaluation questionnaire: both the intervention and placebo product is evaluated using a self-report questionnaire. The evaluation questionnaire concerns overall liking, side effects related to consumption, taste fatigue, texture, dosage and manageability.

Control for confounders: other registrations and precautions

Actions are taken to actively reduce or register known or possible confounders. Thus, at baseline, confounders such as admission diagnosis, chronic diseases, nutritional risk (NRS 2002),³⁶ sarcopenia,³⁷ depression³⁸ and mobility^{39 40} are evaluated, among others. Nutritional risk is determined based on a combination of factors: unintended weight loss within the last 3 months, loss of appetite within the last week, body mass index, disease severity and age. Patients screened to be at risk are expected to benefit from nutritional intervention. Sarcopenia is assessed according to the definition proposed by the European Working Group on Sarcopenia in Older People. This is based on the assessments of LBM (measured by BIA), muscle strength (measured by HGS) and physical performance (measured by 4m GS). Furthermore, besides register vitamin D intakes, throughout the study, the following two measures are collected on an ongoing basis.

Protein and energy intake

During hospitalisation, the participants' protein (g/kg) and energy (kJ/kg) intake will be registered for 4 days or shorter if the participants are discharged. The hospitals' food and drink registration schemes will be used. Participants will be asked to fill in the food registration schemes themselves with help from the nurses and study investigators. The participant's body weight at inclusion will be used to calculate the intake per kg body weight. During the 12-week posthospital intervention the participants protein and energy intake will be estimated based on the average of four 24-hour dietary recall interviews performed at study week 3, 6, 9 and 12 at home visits, or by phone if the participant are no longer compliant in the study with regard to the intervention products and the RT. As the home visits will be planned in collaboration with the participants and has to be fitted into other study tasks and visits, these practicalities decide what day of the week the recall interview is covering. To minimise the risk of recall bias, a checklist of specific foods and beverages will be used to verify the reported intake. Furthermore, when interviewing face to face, picture series of portion sizes of different foods will be used to estimate the amounts ingested.⁴¹ The foods and drinks will be entered in the software program Madlog Vita to calculate the intake of protein (g) and energy (kJ). Four days of registration/dietary recalls are considered adequate to assess this information with a high correlation.⁴² An average of the participant's body weight after discharge and in week 12 will be used to calculate the intake per kg body weight.



The cut-off for suspecting under-reporting will be evaluated retrospectively on an individual basis taking any illness, readmissions, loss of body weight, activity level and so on into account.

Daily activity level

In a semistructured interview, the participants are asked about exercise-related activities besides the RT programme. This is reported four times after discharge in study week 3, 6, 9 and 12 at home visits or by phone if the participant is no longer compliant in the study with regard to the intervention products and the RT. Depending on the answers given, the participants will be divided into activity levels from 1 to 5 after predefined criteria, inspired by Saltin and Grimby.⁴³ The scale is ordinal, and activity level 1 represents the least active and level 5 represents the most active. It is the time used on different activities and the intensities of these (low, moderate or high) that determine the activity level.

Statistics

Power calculation

The primary endpoint is muscle strength measured by the 30s CST. The clinical relevant difference for this test is found to be 2.0–2.6, when assessed in older populations with hip and knee osteoarthritis.²⁵ Jones *et al*²³ has used the standardised 30s CST on community-dwelling older people and found an SD of 3.0 and 3.6 for people in the age range of 70–79 years and 80–89 years, respectively.²³ This gives a pooled SD of 3.31, which is used in this power calculation, and it corresponds well with measures of SD found in the modified test version.⁴⁴

In order to be able to detect a difference of 2.0, with a power of 80% and a two-sided alpha error of 0.05, the required sample size is 80 participants in each group, given an anticipated combined rate of dropouts and non-compliance of 45%. This rate is chosen since studies with resistance training in older adults both while hospitalised⁴⁵ and in a community-dwelling setting⁴⁶ have experienced dropouts of 30%. Moreover, an additional 15% is added to account for participants with a low compliance to the intervention to be able to maintain the statistical power of the study in the intention-to-treat analysis as well as in the per-protocol analysis. For practical reasons, if possible within the time schedule, 55 participants will be included at each of the three sites, resulting in a total inclusion of 165 participants.

Feasibility of recruitment and sample size

The three hospitals where recruitment is going to take place had between 525 and 687 geriatric patients in year 2014, with a median LOS ranging from 8 to 11 (5–16) days. The median age for women was in the range of 84–87 years and 83–84 years for men.⁴⁷ To meet the timetable, the expected recruitment rate is a minimum of two participants per week which, based on these data, is considered realistic.

Statistical tests

The primary analysis will be performed by the intention-to-treat principle. In addition, a predefined per-protocol analysis will be performed including participants with a high compliance only (consumption of the intervention product $\geq 75\%$). Furthermore, endpoints will be compared adjusting for randomisation bias (defined as $P < 0.05$ between groups) and confounding factors (total activity level and total protein and energy intake). Analysis will be done both with and without imputation techniques for missing values, but dropouts will be encouraged to participate in follow-up examinations, including interviews concerning dietary intake and activity level. Sensitivity analysis will be performed without outliers, defined as a value of 3 SD above or below the mean. To investigate whether the intervention will have different impacts in different groups of patients, for example, those who are at nutritional risk or sarcopenic, subgroup analysis will be performed looking at treatment effect in the subgroups and interactions between treatment effect and subgroups. Furthermore, observational analysis will be performed, investigating the importance of total protein and energy intake and total activity level on outcome measures. The two groups will be compared looking at the hospitalisation intervention period and the 12-week postdischarge intervention period both separately and as a whole.

Results will be presented as median (range) or mean (SD or 95% CI) and number (absolute frequencies) for continuous and categorical variables, respectively. Inspection for normality will be done by visual inspection (Q–Q plot), and parametric or non-parametric statistical tests will be used in accordance with the distribution of the variables. Statistical comparisons will be made between the two groups by using the Mann-Whitney U-test or Student's t-test for continuous variables and the χ^2 test or Fisher's exact test (in case of expected cell count < 5) for the comparison of categorical variables. Analysis of covariance will be used for continuous outcomes and binary logistic regression for binary outcomes if/when adjusting for confounders and testing for subgroup interaction. The Spearman rank correlation test or general linear model will be used to test for correlations between independent variables. All tests are two tailed, and an alpha level of $P < 0.05$ will be used to determine statistical significance in all analyses.

With regard to the primary endpoint, 30s CST, the changes in performance from baseline (both with and without pooling standardised and modified test results) will be measured and compared between the two groups. Furthermore, performance will be scored into one of three categories: (1) ability to rise from the chair with arms folded across the chest; (2) ability to rise from the chair using the arm rest; and (3) not able to rise independently from the chair. Also, compared with baseline, performance will be scored into either 'better', 'worse' or 'unchanged'.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki. Thus, precautions will be taken to protect the privacy and confidentiality of research subjects. The study is registered in the clinical.trial.gov database (NCT02717819). Any amendments to the protocol will be made public at clinical.trial.gov. All participants receive written and oral information from study investigators about all relevant aspects of the study before making decision about participation, and they are informed that they can withdraw from the study at any time. The participants receive no payment and will have no expenses associated with participation in the study. There are no expected risks associated with participation, and we expect each participant to benefit from the RT. The results of the study will be published in international peer-reviewed journals and presented at national and international congresses and symposiums.

DISCUSSION

This study investigates the effect of protein supplementation in addition to offering RT among older adults while admitted to the geriatric ward and after discharge. The acutely ill 'geriatric patient' is a heterogeneous patient group with various (non-surgical) diseases and often existing comorbidities. The goals are to counteract sarcopenia, maintain or improve physical function and reduce healthcare costs in this specific population. Thus, with this study, we wish to add knowledge about effective secondary prevention and interdisciplinary rehabilitation strategies to the large population of acutely ill older adults admitted to hospital. The eligibility criteria are very broad; however, the weakest patients (no stand function) are excluded, as these will not be able to participate in a RT programme and perform the endpoint measurements. The participants in the current study are included within 3 days of admission. It is possible that the weakest geriatric patients with no stand function, currently excluded, will gain their stand function later during their hospitalisation (>3 days). Thus, the results from the current study may also be relevant to this group of patients, although not examined. A common confounder is that people agreeing to participate in an intervention trial are more motivated to lifestyle changes, which is an important factor for the compliance and possible success of this intervention.

Use of placebo beverages allows blinding of participants and researchers. Thus, performance and detection bias are minimised. Another strength is the randomisation procedure, which will limit selection bias and hopefully balance different confounders that could potentially influence the results. The multicentre trial design furthermore increases the generalisability of the results. The activity and dietary interviews are conducted in order to be able to correct statistically for differences in protein intake and activity levels between groups. In addition, it

will also enable us to investigate the importance of overall protein and energy intake on the results.

The majority of older adults in Denmark take vitamin D supplements as recommended by the Danish Health Authority.²¹ Studies have shown that vitamin D has an independent positive effect on muscle strength.⁴⁸ In order to investigate the effect of the protein supplementation alone, vitamin D supplements will be given to all participants with serum vitamin D levels ≤ 100 nmol/L at inclusion to ensure similar vitamin D intakes. Another reason for ensuring that all participants are supplemented with vitamin D is that the protein-enriched beverage approximately halfway through the intervention period will have vitamin D added to the product. However, the fortification level is quite low, adding an extra amount of only 3.5 µg vitamin D per day from the beverages which, for example, corresponds to 13 g of salmon.⁴⁹ Also, compared with the daily vitamin D supplementation of minimum 20 µg (some older adults take even higher amounts, as prescribed by their doctor), it is considered insignificant.

In regard to ensure compliance to the RT programme, it is a weakness of the study that the RT at home after discharge is not supervised. However, an aim of the current study is to test the effect of an interdisciplinary rehabilitation regime that is cost-effective and could easily be implemented. Supervised RT four times per week would have required a lot of resources, which most likely would not be possible to implement in the real world. If a positive effect is found from an intervention consisting only of extra protein consumption and self-training after discharge, then potential implementation in clinical practice will be more feasible and likely. The current study can also give valuable insights into which subgroups of the geriatric patients that would be able to benefit from a rehabilitation regime based on self-training and protein intervention. The high rate of readmissions to hospital among older adults⁵⁰ indicates that there is room for improvement in regard to secondary prevention strategies.

The specific endpoints included in the current study were chosen in order to be suitable, feasible and valid for this specific population of older adults. Thus, a low amount of missing data is expected due to low feasibility. The 30s CST, DEMMI and Barthel-100 are part of the normal routine tests for geriatric patients admitted to the medical departments (they are included in The Danish National Geriatric Data Base), and all tests and questionnaires are developed and/or validated in older adults.^{28 32–34} Furthermore, the Danish Board of Health recommends the use of 30s CST, 4m GS, MMSE and EQ-5D-3L as tests in older geriatric patients.²⁹ Also, LBM, measured by BIA, has been proposed as a feasible measurement tool in this population,^{3 51} and a portable BIA is a practical tool suitable for home visits.

Specifically for the primary endpoint, the 30s CST has been shown to be a reliable and valid indicator of lower body strength in generally active, community-dwelling older adults when validated against maximum



weight-adjusted leg-press performance.²³ The standardised 30s CST version has been shown to have low feasibility (54%) in acutely admitted old medical patients and to have lower inter-rater reliability than in medically stable patients. However, the modified 30s CST has been shown to be both feasible and having a high inter-rater reliability.²⁸ Thus, we believe that all participants will be able to perform either the standardised or the modified version, supported by the inclusion criteria, that only patients who can stand independently are recruited, eliminating those in poorest conditions. This is also in accordance with experience from our former intervention studies performed in geriatric patients^{52 53} and also applies to the other secondary endpoints.

For the secondary endpoint, LBM measured by a portable BIA, Moon *et al*⁵¹ have shown that single frequency BIA in elderly men and women (72 men and women, >65 years) correlate well with dual-energy X-ray absorptiometry (DXA) measurements, as well as the four-compartment model, at single time points as well as for tracking changes in LBM. They concluded that DXA and BIA can be used interchangeably as valid methods to measure LBM when looking at a population basis of more than 15–22 people.⁵¹ Furthermore, Karelis *et al*⁵⁴ have validated the portable, dual-frequency InBody-230 BIA against DXA in a healthy mixed population (145 men and women, 44.6±20 years) and found a significant high correlation when looking at fat mass, percent body fat and total LBM.⁵⁴ Thus, it is expected that using the InBody-230 BIA equipment, besides being practical in regard to home visits, will be a reasonable valid method to assess total muscle mass in a population of 165 older adults.

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Contributors AMB prepared the grant application. AMB and JG conceived the overall study draft, and JG created the detailed study protocol. AA, AV, BC, TWK and CB participated in its design and coordination. JG and research assistants collected the data under the supervision of AA, AV, AMB, BC and CB. JG drafted the manuscript. All authors reviewed the article critically and contributed significantly to the final content. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Research Ethic Committee of the Capital Region of Denmark. The study has been approved by the Danish Regional Ethical Committee (reference no. H-16018240) and the Danish Data Protection Agency (reference no. HGH-2016-050).

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Data sharing statement Data collection is still ongoing. Thus, no additional unpublished data are currently available.

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Protein-enriched, milk-based supplement to counteract sarcopenia in acutely ill geriatric patients offered resistance exercise training during and after hospitalisation: study protocol for a randomised, double-blind, multicentre trial

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